Synthesis and anti-microbial screening of novel schiff bases of 3-amino-2-methyl quinazolin 4-(3H)-one

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ABSTRACT

In the present study, novel Schiff bases were synthesized by condensation of 3-amino-2-methyl quinazolin-4-(3H)-ones with different aromatic aldehydes. The 3-amino-2-methyl quinazolin-4-(3H)-one was synthesized from anthranilic acid via the 2-methyl benzoxazin-4-one. The chemical structures of the synthesized compounds were confirmed by means of Infrared (IR), ^{1}H-NMR, ^{13}C-NMR, Mass spectral, and Elemental analysis. These compounds were screened for anti-bacterial (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, and *Klebsiella pneumoniae* ATCC 11298)) and anti-fungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities, using the paper disk diffusion technique. The minimum inhibitory concentrations (MIC) of the compounds were also determined by the agar streak dilution method. Most of the synthesized compounds exhibited significant anti-bacterial and anti-fungal activities. Among the synthesized compounds, 3-(4-hydroxy benzylideneamino)-2-methyl quinazolin-4(3H)-one 4g and 4c was found to exhibit the highest anti-bacterial activity and 3-(4-hydroxy-3-methoxy benzylideneamino)-2-methyl quinazolin-4(3H)-one 4k exhibited the highest anti-fungal activity.

Key words: 3-amino-2-methyl quinazolin-4-(3H)-one, anti-bacterial, anti-fungal, Schiff base

INTRODUCTION

Quinazolin-4-(3H)-ones have been reported to possess a wide range of biological activities such as anti-microbial.[1-5] analgesic,[6,7] anti-inflammatory,[8] anti-convulsant,[9,10] anti-cancer,[11,12] anti-tubercular,[13,14] anti-malarial,[15] and anti-viral[16,17] activities. Quinazolin 4-(3H)-ones, with substitution at the third position, has been reported to be associated with antimicrobial properties.[18,19] The various substituents at the third position of quinazolin-4(3H)-one that have been reported, are various substituted phenyl ring moieties, bridged phenyl rings, heterocyclic rings, and the aliphatic system. In addition, in general schiff bases, the presence of pharmacophores like $-NO_2$, phenolic OH, -Cl, $-CH_3$, and $-OCH_3$ are reported to possess anti-microbial activities. These observations has led to the conception that a novel series of Schiff bases of 3-amino-2-methyl quinazolin-4-(3H)-ones 4a-4l have been synthesized using different aromatic aldehydes by condensation and their chemical structure is confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral and Elemental analysis. These compounds have been screened for their anti-bacterial activity against four gram positive bacteria (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, and *Bacillus cereus* ATCC 11778), three gram negative bacteria (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, and *Klebsiella pneumoniae* ATCC 11298), and anti-fungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities, using the paper disk diffusion technique. The minimum inhibitory concentrations (MIC) of the compounds were also determined by the agar streak dilution method.

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MATERIALS AND METHODS

The melting points were taken in an open capillary tube and were uncorrected. The IR spectra of the compounds were recorded on an ABB Bomem FT-IR spectrometer MB 104 with KBr pellets. The ^{1}H (300 MHz) and ^{13}C-NMR (300 MHz) spectra were recorded on a Bruker 300 NMR spectrometer (with TMS for ^{1}H and $CDCl_3$ for ^{13}C as internal references). Mass spectra were recorded on a Shimadzu GC MS QP 5000.

Microanalyses were obtained with an elemental an Analyses system GmbH VarioEL V300 element analyzer. The purity of the compounds was checked by thin layer chromatography (TLC) on pre-coated SiO_2 gel (HF_{254}, 200 mesh) aluminium plates (E Merck) using ethyl acetate : n-hexane (20 : 80) and visualized in an ultraviolet (UV) chamber. The reagent grade chemicals were purchased from S.D. Fine-Chem Limited, Mumbai, and Qualigens Fine Chemicals, Mumbai, and purified by either distillation or recrystallization, before use.

Chemistry

In the present study anthranilic acid 1 was treated with acetic anhydride to form 2-methyl benzoxazin-4-one 2, which further reacted with hydrazine hydrate resulting in 3-amino-2-methyl quinazolin-4-(3H)-one 3. Compound 3 was subjected to react with various aromatic aldehydes in the presence of ethanol as a solvent, to form schiff bases.

General Method of Synthesis (4a-4l)

The 3-amino 2-methyl quinazolin-4(3H)-one 3 was prepared according to the reported literature.[18] Equimolar quantities (0.01 mol) of 3-amino 2-methyl quinazolin 4-(3H)-one and aromatic aldehydes were dissolved in 20 ml of ethanol, refluxed for eight hours, and then kept aside for three days. The product that separated out was filtered, dried, and recrystallized from absolute ethanol.

Anti-microbial Screening

The standard strains were procured from the American Type Culture Collection (ATCC), Rockville, USA, and the pathological strains were procured from the Department of Microbiology, CEEAL Analytical Lab, Chennai, India. All test compounds and standard drugs were dissolved in dimethyl formamide for screening the anti-microbial activity. All the synthesized compounds were screened for anti-bacterial and anti-fungal activities by the paper disk diffusion technique. The anti-bacterial activity of the compounds were evaluated against four gram positive bacteria (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, and *Bacillus cereus* ATCC 11778) and three gram negative bacteria (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, and *Klebsiella pneumoniae* ATCC 11298), using the nutrient agar medium (Hi-Media Laboratories, India). The anti-fungal activities of the synthesized compounds were evaluated against two fungi (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) using the Sabouraud dextrose agar medium (Hi-Media Laboratories, India). The minimum inhibitory concentrations (MIC) of the compounds were also determined by the agar streak dilution method.

Paper Disk Diffusion Technique

The sterilized[20] (autoclaved at 120°C for 30 min) medium (40 – 50°C) was inoculated (1 ml/100 ml of medium) with the suspension (10^5 cfu/ml) of the microorganism (matched to the McFarland barium sulfate standard) and poured into a petridish to give a depth of 3 – 4 mm. The paper impregnated with the test compounds dissolved in dimethylformamide (100 µg/disk) and was placed on the solidified medium. The plates were pre-incubated for one hour at room temperature and incubated at 37°C for 24 and 48 hours for anti-bacterial and anti-fungal activities, respectively. Ciprofloxacin (100 µg/disk) and Ketoconazole (100 µg/disk) were used as the standards for anti-bacterial and anti-fungal activities, respectively. The observed zone of inhibition is presented in Table 1.

Minimum Inhibitory Concentration

The Minimum inhibitory concentration (MIC)[21] of the compound was determined by the agar streak dilution method. A stock solution of the synthesized compound (100 µg/ml), in dimethylformamide, was prepared and graded quantities of the test compounds were incorporated in a specified quantity of molten sterile agar (nutrient agar for anti-bacterial activity and Sabouraud dextrose agar medium for anti-fungal activity). A specified quantity of the medium (40 – 50°C) containing the compound was poured into a petridish to give a depth of 3 – 4 mm, and allowed to solidify. A suspension of the microorganism were prepared, to contain approximately 10^5 cfu/ml, and applied on the plates with serially diluted compounds in dimethylformamide, to be tested, and was incubated at 37°C for 24 and 48 hours for bacteria and fungi, respectively. The MIC was considered to be the lowest concentration of the test substance, exhibiting no visible growth of bacteria or fungi on the plate. The observed MIC is presented in Table 1.

RESULTS AND DISCUSSION

Chemistry

Infrared, ^{1}H-NMR, ^{13}C-NMR, Mass spectra, and Elemental analysis were consistent with the assigned structures. The optical activities of the compounds were not checked.

3-Amino 2-methyl Quinazolin-4(3H)-one (3)

Yield: 73%; m.p.141 – 143°C; IR (KBr, cm^{-1}): 3030 (Ar-CH), 2927 (CH in CH_3), 1716 (C=O), 1464 (C=C), 1332 (N-H). ^{1}H-NMR ($CDCl_3$) δ: 7.41-7.82 (m, 4H; C_5,C_6,C_7,C_8,Ar-H), 1.94 (s, 2H; -NH_2), 0.97 (s, 3H; -CH_3). ^{13}C-NMR ($CDCl_3$) δ: 164.2 (C_2), 161.7 (C_4), 133.6 (C_7), 128.2 (C_5), 127.6 (C_6), 122.3 (C_8), 18.9 (-$\underline{C}H_3$). EI-MS m/z (M+): 175 (Calcd. for $C_9H_9N_3O$; 175.18). Anal. Calcd. for $C_9H_9N_3O$; C, 61.70; H, 5.18; N, 23.99. Found: C, 61.65; H, 5.18; N, 23.88 [Figure 1].

3-(Benzylideneamino)-2-methyl quinazolin-4-(3H)-one (4a)

Pale yellow crystal; Yield: 80%; m.p. 153 – 155°C; IR (KBr, cm^{-1}): 3018 (Ar-CH), 2920 (CH in CH_3), 1720 (C=O), 1510 (C=N), 1460 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.05 (s, 1H; -N=C$\underline{H}$-), 7.19-7.88 (m, 9H; C_5,C_6,C_7,C_8,$C_{2'}$,$C_{3'}$,$C_{4'}$,$C_{5'}$,$C_{6'}$,Ar-H), 0.86 (s, 3H; C_2, -CH_3). ^{13}C-NMR ($CDCl_3$) δ: 164.2 (C_2), 160.1 (C_4), 143.3 (-N=$\underline{C}$H-), 133.3 (C_7), 131.4 ($C_{4'}$), 129.4 ($C_{2'}$ and

Table 1: Anti-microbial activity of the synthesized compounds

Compounds	*In vitro* activity — zone of inhibition [100 µg/disk] in mm (MIC in µg/ml)								
	S.aureus	*S. epidermidis*	*M. luteus*	*B. cereus*	*E. coli*	*P. aeuriginosa*	*K. pneumoniae*	*A. niger*	*A. fumigatus*
4a	15 (25.2)	19 (20.4)	13 (27.8)	16 (19.2)	18 (21.9)	17 (19.8)	14 (23.6)	13 (29.1)	11 (30.6)
4b	19 (19.3)	18 (21.2)	20 (16.3)	17 (15.3)	18 (19.2)	18 (18.6)	15 (21.8)	19 (17.9)	16 (19.9)
4c	21 (10.4)	25 (9.8)	23 (11.2)	19 (12.1)	21 (14.8)	20 (10.8)	22 (13.9)	20 (13.3)	19 (13.6)
4d	20 (13.2)	20 (17.6)	17 (20.6)	18 (16.7)	17 (19.0)	17 (19.7)	17 (19.6)	18 (21.3)	17 (18.8)
4e	19 (13.6)	23 (14.8)	20 (12.4)	17 (17.1)	20 (14.4)	20 (12.6)	24 (11.8)	23 (13.8)	18 (14.2)
4f	22 (11.8)	18 (20.2)	17 (19.6)	16 (21.2)	19 (18.6)	16 (18.6)	20 (17.6)	19 (20.2)	18 (17.9)
4g	24 (9.2)	27 (10.2)	24 (11.6)	21 (9.6)	23 (12.1)	21 (11.8)	25 (10.6)	24 (13.1)	19 (14.5)
4h	20 (12.8)	18 (18.6)	20 (17.6)	16 (20.2)	22 (14.1)	16 (21.4)	22 (15.7)	24 (12.8)	17 (18.6)
4i	22 (10.6)	24 (10.4)	21 (12.1)	18 (13.7)	22 (13.2)	19 (13.4)	22 (14.3)	22 (14.1)	15 (20.8)
4j	19 (18.2)	22 (13.8)	19 (18.7)	17 (18.6)	20 (19.1)	16 (20.8)	17 (18.6)	18 (17.7)	18 (16.1)
4k	21 (12.5)	25 (10.3)	22 (14.1)	18 (10.6)	21 (13.4)	21 (11.8)	23 (12.8)	22 (12.2)	20 (12.9)
4l	17 (22.8)	14 (24.0)	18 (19.7)	15 (20.7)	19 (20.2)	14 (21.6)	16 (18.9)	15 (21.8)	13 (24.8)
Ciprofloxacin	25	29	27	23	29	25	27	-	-
Ketoconazole	-	-	-	-	-	-	-	29	26
DMF	-	-	-	-	-	-	-	-	-

$C_{6'}$), 128.9 ($C_{3'}$ and $C_{5'}$), 128.6 (C_5), 127.1 (C_6), 19.8 (-$\underline{C}H_3$). EI-MS m/z (M+): 263 (Calcd. for $C_{16}H_{13}N_3O$; 263.29). Anal. Calcd. for $C_{16}H_{13}N_3O$; C, 72.99; H, 4.98; N, 15.96. Found: C, 72.95; H, 4.96; N, 15.92.

3-(4-Methoxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4b)

Cream solid; Yield: 72%; m.p. 191 – 194°C; IR (KBr, cm^{-1}): 3046 (Ar-CH), 2912 (CH in CH_3), 1724 (C=O), 1514 (C=N), 1462 (C=C), 1124 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 8.07 (s, 1H; -N=C$\underline{H}$-), 6.81-7.92 (m, 8H; $C_{5'}$,$C_{6'}$,C_7,C_8,$C_{2''}$,$C_{3''}$,$C_{5''}$,$C_{6''}$,Ar-H), 3.70 (s, 3H; -OC$\underline{H}_3$), 0.79 (s, 3H; -C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.9 (C_2), 160.2 (C_4),143.2 (-N=$\underline{C}$H-), 133.2 (C_7), 163.1 ($C_{4'}$), 130.1 ($C_{2'}$ and $C_{6'}$), 128.6 (C_5), 127.3 (C_6), 126.2 ($C_{1'}$), 122.2 (C_8), 114.3 ($C_{3'}$ and$C_{5'}$), 55.6 (-O$\underline{C}H_3$), 20.2 (-$\underline{C}H_3$). EI-MS m/z (M+): 293 (Calcd. for $C_{17}H_{15}N_3O_2$; 293.31). Anal. Calcd. for $C_{17}H_{15}N_3O_2$; C, 69.61; H, 5.15; N, 14.33. Found: C, 69.58; H, 5.14; N, 14.28.

3-(2-Hydroxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4c)

Pale yellow solid; Yield: 66%; m.p. 173 – 175°C; IR (KBr, cm^{-1}): 3040 (Ar-CH), 2915 (CH in CH_3), 1722 (C=O), 1514 (C=N), 1457 (C=C) 1350,1205 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 7.99 (s, 1H; -N=C$\underline{H}$-), 6.78-7.88 (m, 8H; $C_{5'}$,$C_{6'}$,C_7,C_8,$C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$,Ar-H), 5.41 (s, 1H; Ar-O$\underline{H}$), 0.82 (s, 3H; -C$\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.4 (C_2), 164.5 ($C_{2'}$) 160.6 (C_4), 142.9 (-N=$\underline{C}$H-), 133.7 (C_7), 132.2 ($C_{4'}$), 130.3 ($C_{6'}$), 128.6 (C_5), 127.4 (C_6), 122.1 (C_8), 121.3 ($C_{5'}$), 118.2 ($C_{1'}$), 116.2 ($C_{3'}$), 20.1 (-$\underline{C}H_3$). EI-MS m/z (M+): 279 (Calcd. for $C_{16}H_{13}N_3O_2$; 279.29). Anal. Calcd. for $C_{16}H_{13}N_3O_2$; C, 68.81; H, 4.69; N, 15.05. Found: C, 68.79; H, 4.61; N, 15.01.

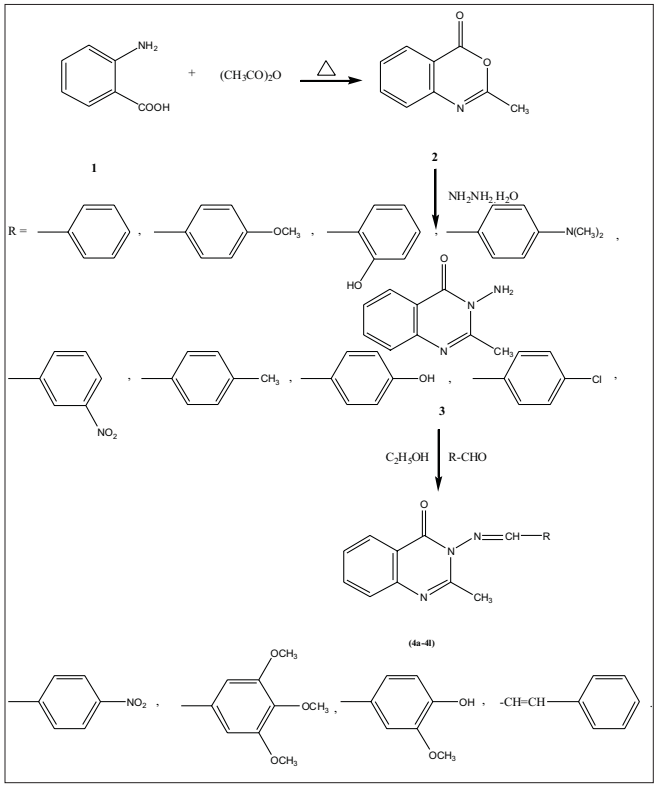

Figure 1: Synthesis of schiff bases of 3-amino-2-methyl quinazolin-4(3H)-one

3-(4-N,N-dimethylaminobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4d)

Bright yellow crystal; Yield: 68%; m.p. 187 – 190°C; IR (KBr, cm^{-1}): 3032 (Ar-CH), 2920 (CH in CH_3), 1720 (C=O), 1518 (C=N), 1453 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.02 (s, 1H; -N=C$\underline{H}$-), 6.75-7.89 (m, 8H; $C_{5'}$,$C_{6'}$,C_7,C_8,$C_{2''}$,$C_{3''}$,$C_{5''}$,$C_{6''}$,Ar-H), 2.86

(s, 6H; -N-(C<u>H</u>$_3$)$_{2'}$, 0.82 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.4 (C_2), 159.2 (C_4) 151.2 ($C_{4'}$), 142.2 (-N=C<u>H</u>-), 133.6 (C_7), 130.3 ($C_{2'}$ and$C_{6'}$), 128.6 (C_5), 127.6 (C_6), 123.2 ($C_{1'}$), 122.3 (C_8), 113.8 ($C_{3'}$ and $C_{5'}$), 55.6 (-OC<u>H</u>$_3$), 20.1 (-C<u>H</u>$_3$). EI-MS m/z (M+): 306 (Calcd. for $C_{18}H_{18}N_4O$; 306.36). Anal. Calcd. for $C_{18}H_{18}N_4O$; C, 70.57; H, 5.92; N, 18.29. Found: C, 70.48; H, 5.94; N, 18.31.

3-(3-Nitrobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4e)

Cream solid; Yield: 65%; m.p. 190 – 194°C; IR (KBr, cm^{-1}): 3017 (Ar-CH), 2922 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1522 and 1335 (N=O), 1450 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.09 (s, 1H; -N=C<u>H</u>-), 7.41-7.92(m, 7H; $C_{5'}$,$C_{6'}$,$C_{7'}$,$C_{8'}$,$C_{4''}$,$C_{5''}$,$C_{6''}$,Ar-H), 0.92 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.9 (C_2), 159.8 (C_4), 148.6 ($C_{3'}$), 143.1 (-N=C<u>H</u>-), 134.3 ($C_{1'}$), 135.3 ($C_{6'}$), 133.6 (C_7), 129.8 ($C_{5'}$), 128.8 (C_5), 127.4 (C_6), 124.2 ($C_{2'}$), 123.2 ($C_{4'}$), 122.4 (C_5), 20.3 (-C<u>H</u>$_3$). EI-MS m/z (M+): 308 (Calcd. for $C_{16}H_{12}N_4O_3$; 308.29). Anal. Calcd. for $C_{16}H_{12}N_4O_3$; C, 62.33; H, 3.92; N, 18.17. Found: C, 62.31; H, 3.83; N, 18.14.

3-(4-Methylbenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4f)

Cream crystal; Yield: 76%; m.p. 164 – 166°C; IR (KBr, cm^{-1}): 3041 (Ar-CH), 2926 (CH in CH_3) 1718 (C=O), 1522 (C=N), 1448 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H; -N=C<u>H</u>-), 7.09-7.81 (m, 8H; $C_{5'}$,$C_{6'}$,$C_{7'}$,$C_{8'}$,$C_{2''}$,$C_{3''}$,$C_{5''}$,$C_{6''}$,Ar-H), 2.36 (s, 3H; -C<u>H</u>$_3$), 0.92 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 164.2 (C_2), 160.3 (C_4), 143.1 (-N=C<u>H</u>-), 133.8 (C_7), 130.8 ($C_{1'}$), 129.4 ($C_{3'}$ and $C_{5'}$), 129.1 ($C_{2'}$ and $C_{6'}$), 128.6 (C_5), 127.4 (C_6), 122.6 (C_8), 24.3 (-C<u>H</u>$_3$), 20.3 (C<u>H</u>$_3$). EI-MS m/z (M+): 277 (Calcd. for $C_{17}H_{15}N_3O$; 277.32). Anal. Calcd. for $C_{17}H_{15}N_3O$; C, 73.63; H, 5.45; N, 15.15. Found: C, 73.53; H, 5.41; N, 15.14.

3-(4-Hydroxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4g)

Pale yellow crystal; Yield: 77%; m.p. 210 – 214°C; IR (KBr, cm^{-1}): 3024 (Ar-CH), 2924 (CH in CH_3), 1722 (C=O), 1514 (C=N), 1454 (C=C), 1355 and 1208 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 7.99 (s, 1H; -N=C<u>H</u>-), 6.82-7.88 (m, 8H; $C_{5'}$,$C_{6'}$,$C_{7'}$,$C_{8'}$,$C_{2''}$,$C_{3''}$,$C_{5''}$,$C_{6''}$,Ar-H), 5.44 (s, 1H; Ar-O<u>H</u>), 0.88 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 165.1 (C_2), 160.4 ($C_{4'}$), 159.2 (C_4), 144.2 (-N=C<u>H</u>-), 134.2 (C_7), 130.5 ($C_{2'}$ and $C_{6'}$), 129.2 (C_5), 127.4 (C_6), 122.8 (C_8), 115.6 ($C_{3'}$ and $C_{5'}$), 20.1 (-C<u>H</u>$_3$). EI-MS m/z (M+): 279 (Calcd. for $C_{16}H_{13}N_3O_2$; 279.29). Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.79; H, 4.64; N, 15.07.

3-(4-Chlorobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4h)

Pale yellow powder; Yield: 74%; m.p. 259 – 263°C; IR (KBr, cm^{-1}): 3036 (Ar-CH), 2932 (CH in CH_3), 1726 (C=O), 1520 (C=N), 1446 (C=C), 729 (C-Cl). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H; -N=C<u>H</u>-), 6.91-7.82 (m, 8H; $C_{5'}$,$C_{6'}$,$C_{7'}$,$C_{8'}$,$C_{2''}$,$C_{3''}$,$C_{5''}$,$C_{6''}$,Ar-H), 0.92 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 163.4 (C_2), 160.8 (C_4), 144.2 (-N=C<u>H</u>-), 136.2 ($C_{4'}$), 133.4 (C_7), 132.5 ($C_{1'}$), 130.8 ($C_{2'}$ and $C_{6'}$), 129.2 ($C_{3'}$ and $C_{5'}$), 128.6 (C_5), 126.9 (C_6), 122.4 (C_8), 19.8 (-C<u>H</u>$_3$). EI-MS m/z (M+): 297 (Calcd for $C_{16}H_{12}ClN_3O$; 297.73). Anal. Calcd. for $C_{16}H_{12}ClN_3O$; C, 64.54; H, 4.06; N, 14.91. Found: C, 64.50; H, 4.01; N, 14.81.

3-(4-Nitrobenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4i)

Yellow crystal; Yield: 75%; m.p. 222 – 225°C; IR (KBr, cm^{-1}): 3048 (Ar-CH), 2926 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1518 and 1342 (N=O), 1452(C=C). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H; -N=C<u>H</u>-), 7.35-7.99 (m, 8H; $C_{5'}$,$C_{6'}$,$C_{7'}$,$C_{8'}$,$C_{2''}$,$C_{3''}$,$C_{5''}$,$C_{6''}$,Ar-H), 0.82 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 165.2 (C_2), 161.2 (C_4), 150.2 ($C_{4'}$), 143.2 (-N=C<u>H</u>-), 140.1 ($C_{1'}$), 134.0 (C_7), 129.4 ($C_{2'}$ and $C_{6'}$), 128.9(C_5), 127.6 (C_6), 122.6 (C_8), 121.2 ($C_{3'}$ and $C_{5'}$), 0.92 (-C<u>H</u>$_3$). EI-MS m/z (M+): 308 (Calcd. for $C_{16}H_{12}N_4O_3$; 308.29). Anal. Calcd. for $C_{16}H_{12}N_4O_3$; C, 62.33; H, 3.92; N, 18.17. Found: C, 62.22; H, 3.94; N, 18.21.

3-(3,4,5,-Trimethoxybenzylideneamino)-2-methyl quinazolin-4-(3H)-one (4j)

Bright yellow powder; Yield: 70%; m.p. 261 – 264°C; IR (KBr, cm^{-1}): 3024 (Ar-CH), 2922 (CH in CH_3), 1724 (C=O), 1514 (C=N), 1463 (C=C), 1132 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 8.10 (s, 1H; -N=C<u>H</u>-), 7.38-7.92 (m, 4H; $C_{5'}$,$C_{6'}$,$C_{7'}$,$C_{8'}$,Ar-H), 6.61 (s, 1H; $C_{2''}$,Ar-H), 6.64 (s, 1H; $C_{6''}$,Ar-H), 3.82 (s, 9H; [OC<u>H</u>$_3$]$_3$), 0.91 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 164.5 (C_2), 160.2 (C_4), 150.8 ($C_{3'}$ and $C_{5'}$), 143.3 (-N=C<u>H</u>-), 141.9 ($C_{4'}$), 135.2 (C_7), 129.9 (C_5), 128.2($C_{1'}$), 127.6 (C_6), 122.6 (C_8), 107.1 ($C_{2'}$ and $C_{6'}$), 56.5 (-OC<u>H</u>$_3$), 21.2 (-C<u>H</u>$_3$). EI-MS m/z (M+): 353 (Calcd for $C_{19}H_{19}N_3O_4$; 353.37). Anal. Calcd. for $C_{19}H_{19}N_3O_4$; C, 64.58; H, 5.42; N, 11.89. Found: C, 64.49; H, 5.38; N, 11.85.

3-(4-Hydroxy-3-methoxybenzylideneamino)-2-methylquinazolin-4-(3H)-one (4k)

Cream solid; Yield: 65%; m.p. 122 – 124°C; IR (KBr, cm^{-1}): 3032 (Ar-CH), 2925 (CH in CH_3), 1722 (C=O), 1518 (C=N), 1455 (C=C), 1352 and 1208 (C-O). ^{1}H-NMR ($CDCl_3$) δ: 7.92 (s, 1H; -N=C<u>H</u>-), 7.42-7.82 (m, 4H; $C_{5'}$,$C_{6'}$,$C_{7'}$,$C_{8'}$,Ar-H), 7.10 (s, 1H; Ar-H), 6.66-6.69 (d, J=6.7 Hz; $C_{5''}$, Ar-H), 7.01-7.05 (d, J=5.8 Hz; $C_{6''}$, Ar-H), 5.12 (s, 1H; Ar-OH), 3.90 (s, 3H; -OC<u>H</u>$_3$), 0.92 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 165.1 (C_2), 161.0 (C_4), 151.2 ($C_{3'}$), 148.2 ($C_{4'}$), 143.4 (-N=C<u>H</u>-), 133.6 (C_7), 128.6 (C_5), 127.6 (C_6), 127.4($C_{1'}$), 122.9 ($C_{6'}$), 122.6 (C_8), 56.2 (-OC<u>H</u>$_3$), 20.2 (-C<u>H</u>$_3$). EI-MS m/z (M+): 309 (Calcd. for $C_{17}H_{15}N_3O_3$; 309.31). Anal. Calcd. for $C_{17}H_{15}N_3O_3$; C, 66.01; H, 4.89; N, 13.58. Found: C, 66.06; H, 4.78; N, 13.62.

3-(3-Phenylallylideneamino)-2-methyl quinazolin-4-(3H)-one (4l)

Lemon yellow crystal; Yield: 75%; m.p. 155 – 157°C; IR (KBr, cm^{-1}): 3019 (Ar-CH), 2916 (CH in CH_3), 1728 (C=O), 1512 (C=N), 1458 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 7.61 (s, 1H; -N=C<u>H</u>-), 7.14-7.88 (m, 9H; $C_{5'}$,$C_{6'}$,$C_{7'}$,$C_{8'}$,$C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$,Ar-H), 6.59-6.62 (d, 1H; J=7.2 Hz; C_6H_5-C<u>H</u>=CH-), 5.61-5.63 (d, 1H; J=6.5 Hz; C_6H_5-CH=C<u>H</u>-), 0.92 (s, 3H; -C<u>H</u>$_3$). ^{13}C-NMR ($CDCl_3$) δ: 164.2 (C_2), 160.6 (C_4), 139.2 (C_6H_5-<u>C</u>H=CH-) 137.6 (-N=<u>C</u>H-), 135.2

($C_{1'}$), 134.6 (C_7), 128.8 (C_5), 128.6 ($C_{3'}$ and $C_{5'}$), 128.1 ($C_{4'}$), 127.6 (C_6), 126.6 (C2′ and C6′), 126.3 (C_6H_5-CH=CH-), 20.2 (-CH_3). EI-MS m/z (M+): 289(Calcd. for $C_{18}H_{15}N_3O$; 289.33). Anal. Calcd. for $C_{18}H_{15}N_3O$; C, 74.72; H, 5.23; N, 14.52. Found: C, 74.36; H, 5.08; N, 14.38.

Anti-microbial Screening

Most of the synthesized compounds exhibited moderate-to-potent anti-microbial activity against the tested microorganisms. Compounds 4g and 4k were found to possess significant anti-bacterial and anti-fungal activity when compared to the standard drug (Ciprofloxacin and Ketaconazole for anti-bacterial and anti-fungal, respectively). Compounds 4c, 4h, 4i, and 4l displayed moderate anti-microbial activity, whereas, the remaining compounds showed lesser activity. The MIC of the synthesized compounds was screened by the agar streak dilution method. All the synthesized compounds exhibited moderate-to-good anti-bacterial and anti-fungal activity, with an MIC range of 9.2 – 30.6 µg/ml. 3-(4-hydroxy benzylideneamino)-2-methyl quinazolin-4(3H)-one 4g was found to exhibit the highest anti-bacterial activity against *S.aureus* (MIC: 9.2 µg/ml), *B.cereus* (MIC: 9.6 µg/ml), *E.coli* (MIC: 12.1 µg/ml), and *K.pneumoniae* (MIC: 10.6 µg/ml). 3-(2-hydroxy benzylideneamino)-2-methyl quinazolin-4(3H)-one 4c was found to exhibit the highest anti-bacterial activity against *S.epidermidis* (MIC: 9.8 µg/ml), *M.luteus* (MIC: 11.2 µgml), and *P.aeruginosa* (MIC: 10.8 µg/ml). 3-(4-hydroxy-3-methoxy benzylideneamino)-2-methyl quinazolin-4(3H)-one 4k exhibited the highest anti-fungal activity against *A.niger* (MIC: 12.2 µg/ml) and *A.fumigatus* (MIC: 12.9 µg/ml).The synthesized compounds were active against all the tested microorganisms, with a range of MIC values for *S.aureus* (9.2 – 25.2µg/ml), *S.epidermidis* (9.8 – 24.0 µg/ml), *M.luteus* (11.2 – 27.8 µg/ml), *B.cereus* (9.6 – 21.2 µg/ml), *E.coli* (12.1 – 21.9 µg/ml), *P.aeruginosa* (10.8 – 21.6 µg/ml), *K.pneumoniae* (10.6 – 23.6 µg/ml), *A.niger* (12.2 – 29.1 µg/ml), and *A.fumigatus* (12.9 – 30.6 µg/ml). The potent anti-microbial activity exhibited by 4c, 4g, and 4k may be due to the incorporation of the electron-donating groups like phenolic OH (at either the second or fourth position of the phenyl ring in the 3-substituted quinazolin-4(3H)-ones) and –OCH_3. The interesting results we observed were that both the electron donating as well as the electron withdrawing groups were found to increase the anti-microbial properties, whereas, the unsubstituted derivatives exhibited a lesser degree of activity. The compound 4g was found to possess anti-bacterial activity almost equivalent to the standard drug, but exhibited considerable anti-fungal activity.

CONCLUSION

In conclusion, the present study highlights the importance of aromatic imino substitution at the third position of the quinazolin-4(3H)-one ring features, responsible for the anti-microbial property, and therefore, may serve as a lead molecule to obtain clinically useful, novel entities, in the new millennium.

REFERENCES

1. Trivedi PB, Undavia NK, Dave AM, Bhatt KN, Desai NC. Synthesis and anti-microbial activity of some heterocyclic compounds. Indian J Chem Br 1993;32:497-500.
2. Kant P. Synthesis and anti-microbial activities of some new 2-substituted 3(1′-aryl-4′-nitrophenyl imidazol-5′-yl) amino quinazolin-4-ones. Indian J Heterocycl Chem 2006;15:221-4.
3. Srivastava MK, Mishra B, Nizamuddin. Pharmacological studies of some 2-methyl 3-(arylthio carbamido) quinazol-4-ones and 2-methyl 3(aryliden carboxamido) quinazol-4-ones. Indian J Chem Br 2001;40:342-4.
4. Mishra P, Panneerselvam P, Jain S. A few 2-methyl quinazolin-4(3H)-ones as anti-microbial agents. J Indian Chem Soc 1995;72: 559-60.
5. Jatav V, Jain SK, Kashaw SK, Mishra P. Synthesis and anti-microbial activity of novel 2-methyl 3(1′,3′,4′-thiadiazolyl) 4(3H)-quinazolinones. Indian J Pharm Sci 2006;68:360-3.
6. Alagarsamy V, Rajasolomon V, Vanikavitha G, Paluchamy V, Ravi Chandran M, Arnold Sujin A, *et al*. Synthesis, analgesic, anti-inflammatory and anti-bacterial activities of some novel 2-phenyl 3-substituted quinazolin-4(3H)-ones. Biol Pharm Bull 2002;25:1432-5.
7. Pannerselvam P, Pradeepchandran RV, Sridhar SK. Synthesis, characterization and biological activities of novel 2-methyl quinazolin-4(3H)-ones. Indian J Pharm Sci 2003;65:268-73.
8. Rani P, Archana, Srivastava VK, Kumar A. Synthesis and anti-inflammatory activity of some new 2,3-disubstituted 6-monosubstituted quinazolin-4(3H)-ones. Indian J Chem Br 2002;41:2642-6.
9. Archana, Srivastava VK, Chandra R, Kumar A. Synthesis of potential quinazolinonyl pyrazolines and quinazolinonyl isoxazolines as anticonvulsant agents. Indian J Chem Br 2002;41:2371-5.
10. Alagarsamy V, Thangathirupathi A, Mandal SC, Rajasekaran S, Vijayakumar S, Revathi R, *et al*. Pharmacological evaluation of 2-substituted (1,3,4)-thiadiazolo quinazolines. Indian J Pharm Sci 2006;68:108-11.
11. El-Hiti GA, Abdel-Megeed MF, Zied TM. Synthesis and reaction of some 3-aryl 2-thioxo quinazolin-4(3H)-ones. Indian J Chem Br 2002;41:1519-22.
12. Murgan V, Thomas CC, Rama Sarma GV, Kumar EP. Synthesis of 2-substituted quinazolin-4(3H)-ones as a new class of anticancer agents. Indian J Pharm Sci 2003;65:386-9.
13. Pattan SR, Krishna Reddy VV, Manvi FV, Desai BG, Bhat AR. Synthesis of N-3[4(4-chlorophenyl thiazol-2-yl) 2-aminomethyl] quinazolin-4(3H)-one and their derivatives for antitubercular activity. Indian J Chem Br 2006;45:1778-81.
14. Nandy P, Vishalakshi MT, Bhat AR. Synthesis and antitubercular activity of mannich bases of 2-methyl 3H-quinazolin-4-ones. Indian J Heterocycl Chem 2006;15:293-4.
15. Lakhan R, Singh OP, Singh RL. Studies in 4(3H)-quinazolinone derivatives as antimalarial. J Indian Chem Soc 1987;64:316-8.
16. Bishnoi A, Saxena R, Srivastava K, Joshi MN, Bajpai SK. Synthesis and biological activity of oxo/thionotriazolo isoquinolinyl quinazolones. Indian J Heterocycl Chem 2006;15:307-8.
17. Pandey VK, Mukesh, Tandon M. Synthesis and antiviral activity of quinazolinyl syndnones. Indian J Heterocycl Chem 2006;15: 399-400.
18. Alagarsamy V, Rajasolomon V, Meena R, Ramseshu VK. Synthesis,

analgesic, anti-inflammatory and anti-bacterial activities of some novel 2-butyl 3-substituted quinazolin-4(3H)-ones. Biol Pharm Bull 2005;28:1091-4.

19. Alagarsamy V, Muruganantham G, Venkateshaperumal R. Synthesis, analgesic, anti-inflammatory and anti-bacterial activities of some novel 2-methyl 3-substituted quinazolin-4(3H)-ones. Biol Pharm Bull 2003;26:1711-4.
20. Gillespie SH. Medical Microbiology-Illustrated. United Kingdom: Butterworth Heinemann Ltd; 1994. p. 234-47.
21. Hawkey PM, Lewis DA. Medical bacteriology: A practical approach. United Kingdom: Oxford university press; 1994. p. 181-94.

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